Cardiovascular Disease Risk Associated With Familial Hypercholesterolemia: A Systematic Review of the Literature

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ABSTRACT

Purpose: The goal of this study was to determine cardiovascular disease (CVD) risk associated with familial hypercholesterolemia (FH).

Methods: A systematic review of the published literature was conducted. All publications describing FH risk from PubMed ("cardiovascular disease risk + familial hypercholesterolaemia," 2004–2015), Internet and Medline search of FH registries, and associated references were screened for FH-related CVD risk in titles, abstracts, and study methods. CVD risk expressed as rates, odds, or ratios of mortality and morbidity were extracted. Each article was reviewed for bias by 2 reviewers within 17 items in 7 categories; a modified Newcastle-Ottawa assessment scale was used for nonrandomized studies.

Findings: The complete literature search identified 712 potential publications: 549 from PubMed (Medline), 150 from registries, and 13 from references. Fourteen articles met the inclusion criteria: 8 from registries in the United Kingdom, the Netherlands, Norway, and Spain; 5 from single hospitals or families in Japan, Denmark, the Netherlands, and the United Kingdom; and a population survey in Denmark. Across studies, attrition bias was low in 22 (80%) of 28 items. Risk of selection bias was high in 35 (63%) of 56 items. Selection bias risk was due to low representativeness and lack of a non-FH comparator group within the same study; detection bias risk was due to variable definitions of CVD outcomes/measurement; and performance bias risk was due to long-term, intensive treatment, the most common limitations for registries. Studies from single hospitals and families lacked generalizability. In contrast, the Danish study revealed a low bias in each of the 4 selection bias criteria and 2 attrition risk criteria. Fatal and nonfatal CVD events were collected in the study. Comparing patients with FH versus non-FH patients, the odds ratios for coronary artery disease were 10.3 (95% CI, 7.8–13.8) and 13.2 (95% CI, 10.0–17.4) in subjects treated and not treated with lipid-lowering therapy, respectively. These ratios fall within the ranges of ratios reported in other studies but are generally higher than the ratios from registries and clinics, in which intensive specialized management is available.

Implications: There is a lack of available data describing CVD risk in patients with FH, and many of the existing studies have biases in their design that could affect their risk estimates. A Danish study had the highest quality based on a predefined quality check list, providing the most credible estimates of the increase in CVD risk in patients with FH. The CVD risk due to FH is high and represents unmet medical need for patients with FH. Further research is warranted to validate the magnitude of risk. (*Clin Ther.* 2016;38:1696–1709) © 2016 The Authors. Published by Elsevier HS Journals, Inc.

Key words: bias, cardiovascular disease, familial hypercholesterolemia, lipid-modifying therapy, risk.

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INTRODUCTION

Familial hypercholesterolaemia (FH) is a genetic disorder characterized by autosomal inheritance in genes related to LDL-C metabolism, which results in lifelong elevation of LDL-C. More than 1500 mutations have been identified in the LDL receptor gene (*LDLR*), as well as mutations in other genes leading the clinical FH phenotype.[1]

The major clinical manifestation of FH results from the prolonged exposure of the vasculature to high levels of LDL-C, which leads to the development of atherosclerotic lesions in the heart, brain, and peripheral arteries.[2] These lesions in the arterial wall gradually progress in size, occupying an increasing proportion of the arterial lumen over time. This scenario in turn results in restriction of blood flow, with clinical symptoms of ischemia, such as angina, developing when $\geq 70\%$ obstruction occurs.[3] However, most acute complications, such as myocardial infarction (MI) and sudden cardiac death, occur in lesions that are not severely obstructed, and the first manifestation of coronary disease is often sudden death or nonfatal MI in one half of men and women. These events occur at a higher frequency and at an earlier age in patients with FH than in patients without FH or patients with polygenetic causes of elevated LDL-C.[4]

The risk of cardiovascular disease (CVD) is affected by additional risk factors, including obesity, diabetes, smoking, hypertension, male sex, and age, as well as risk factors that are in addition to the risk associated with increased LDL-C in both FH patients and non-FH patients.[1] The interaction of these additional risk factors in FH compared with non-FH patients is not well understood or studied.

The genetic mutation leading to FH is present at birth with the increased level of LDL-C being asymptomatic until the occurrence of end-organ damage. Hence, patients can come to the attention of the health care system through the development of end-organ damage, the serendipitous performance of a LDL-C measurement, or an active screening program, in which individuals are generally targeted for screening because of a family association or a general population-level screening program.[5] Early management and primary CVD prevention, with aggressive treatment of LDL-C levels with lipid-modifying therapy and modification of other risk factors, have been found to be effective.[6] The effectiveness of primary prevention has led to the introduction of screening programs in some countries and a call for increased awareness by the European Society of Cardiology.[7] Screening uses clinical criteria for FH, and no genetic mutations are identified in many patients who have a clinical phenotype of FH.[8]

Estimating the absolute increase in cardiovascular risk resulting from FH is complicated. Case ascertainment is likely to be biased toward patients experiencing symptoms and cardiovascular events. When FH is identified, modification of risk factors, particularly LDL-C, will reduce the risk of cardiovascular events. Recent evidence has also demonstrated an increased risk of raised concentrations of the LDL-like particle plasma lipoprotein(a).[9] Comparison populations will likely be diluted by unidentified patients with FH, leading to an overestimation of cardiovascular risk in the comparison group. Prevalence of risk factors such as smoking, obesity, and hypertension, as well as their management and impact, will also likely differ between patients with FH and the general population, adding further complexity to calculating the absolute risk of CVD due to FH.[10]

The rate of increase in cardiovascular risk associated with FH is important in determining the likely adoption of screening and primary prevention programs for the management of FH, as well as new therapies recently approved to better manage patients with FH and their CV risk.[11]

With these complexities in mind, the goal of the present study was to examine the literature systematically and to quantify, if possible, the excess risk of cardiovascular disease in FH, assessing the adequacy and availability of the evidence according to a study quality checklist to support health technology assessment decision-making.

MATERIALS AND METHODS

A systematic search of the literature was undertaken to identify studies that examined the risk of cardiovascular disease in FH. A Medline search using the search string "((((Cardiovascular Disease Risk + Familial Hypercholesterolaemia) NOT Nursing) AND English [Language]) NOT randomized controlled trials) NOT reviews [Publication Type]" was performed for articles published between January 1, 2004, and December 31, 2015. An additional targeted

search of publications from FH registries was conducted for reported estimates of increased risk. The references of these articles were then reviewed to identify additional studies, including a prior review conducted by Austin et al.[1] Publication titles and abstracts were screened for content, and the resulting articles were retrieved for full-text review. Publications that included any measure of CVD risk (risk, rates, odds, or ratios of mortality and morbidity) in patients with FH were the outcomes of interest of this review. Studies were excluded if they had no CVD risk estimate in FH or no CVD risk estimate in FH versus non-FH. Studies were also excluded if they were not specific to FH (using a prospective definition of FH) or included only a subgroup of patients with FH. Review articles and letters to the editor were also excluded.

To measure the potential for bias of each study, we developed a bias assessment form based on the Cochrane Handbook report of low risk, unclear risk, and high risk of bias.[12] Because the studies within this search were nonrandomized trials, we adapted the Newcastle-Ottawa criteria for nonrandomized studies to assess study quality.[13] The Newcastle-Ottawa criteria for cohort studies broadly assess how subjects are selected, the comparability of the cohorts, and how outcomes are assessed. These broad categories are divided into 6 areas of potential bias: selection bias, performance bias, detection bias, attrition bias, confounding, and reporting bias. An additional category of "other biases" allows for the capture of any bias not covered by the defined categories. Selection bias assesses where eligibility criteria are explicitly described, the selection of the eligible population from the target population, similarities in exposed and unexposed groups, and exclusion of participants. Performance bias assesses the ascertainment of exposure and outcomes, temporal sequence, and concurrent interventions or unintended exposures. Detection bias assesses the blinding of assessors, valid and reliable measurement of exposure status and outcomes, and exposure durations. Attribution bias assesses missing data across exposed and unexposed groups. Confounding bias assesses valid and reliable measurement of confounders and controlling for confounders. Reporting bias assesses post hoc analyses. A worksheet with guided questions for the reviewer provided multiple criteria to assess bias risk with 17 individual bias assessments being made for each study (Table I). Data entry and descriptive statistics for the study characteristics and bias assessments were captured by using Microsoft Excel 2010 (Microsoft Corporation, Redmond, Washington).

The bias assessments were performed by 2 reviewers (B.W. and G.K.) independently, and reconciliation of any differences occurred by mutual agreement and discussion. Reviewers applied bias assessments to studies with reference to the specific objective of estimating the cardiovascular risk, even if there were multiple objectives within the article and when the primary reason for the research was for an alternate purpose. This approach was particularly relevant for registries in which their primary purpose is one of patient management rather than formal risk calculation, but bias assessment for the risk calculation remained the focus for the purposes of the present analysis. Bias risk assessments were coded as high risk, low risk, and unclear risk for each study by using bias assessment criteria.

RESULTS

The complete literature search identified 712 potential publications: 549 from PubMed (Medline), 150 from registries, and 13 from references. After title and abstract review, 29 articles were identified as likely to contain cardiovascular risk estimates and were retrieved for full-text review. Of these, 14 studies contained estimates of the rate of increased risk of CVD in FH and are summarized in the present study (Table II).[14–27] Eight studies were based on registries in the United Kingdom, the Netherlands, Norway, Japan and Spain; 5 were from single hospitals or families in Denmark, Netherlands, and United Kingdom; and 1 was based on a population survey in Denmark (Figure 1).

Trends in risk assessment were observed by bias type (Table I). When bias risk was examined across the studies, selection bias was the largest potential threat with 63% (35 of 56) of the selection bias criteria categorized as high risk. Performance bias was also an issue, in which 14% (6 of 42) of the criteria were high risk and 26% (11 of 42) were unclear risk. Unclear risk was prevalent in both detection bias and confounding bias, with 34% (19 of 56) of the detection bias criteria and 64% (18 of 28) of the confounding bias criteria identified as unclear risk. In contrast, attrition bias and confounding bias were not

Table I. Summary of quality/risk of bias assessment of the included studies.

Population survey–based studies

Bias category	Selection				Performance			Detection				Attrition		Confounding		Reporting	Other	
Study	Eligibility criteria explicitly described	Selection of eligible population from the target population	Similarities of exposed and unexposed groups	Exclusion of participants from analysis of the outcome	Ascertainment of exposure and outcome	Temporal sequence	Concurrent interventions or unintended exposures	Blinding of assessors	Valid and reliable measurement of exposure status	Valid and reliable measurement of outcomes	Exposure durations	Missing data across exposed and unexposed groups	Accounting for missing data	Control for confounders	Valid and reliable measurement of confounders	Post-hoc Analyses	Other biases	High bias count × study
Population-survey -based studies																		
Benn et al (2012)[14]																		0
Registry -based studies																		
Mabuchi et al (1989)[15]																		6
Simon Broome Registry (1991)[16]																		4
Simon Broome Registry (1999)[17]																		4
Alonso et al (2000)[18]																		11
Neil et al (2008)[19]																		4
Versmissen et al (2008)[20]																		3
Besseling et al (2014)[21]																		4
Mundal et al (2014)[22]																		5
Hospital-based and family -based studies																		
Jansen et al (1967)[23]																		3
Slack et al (1969)[24]																		9
Sijbrands et al (2000)[25]																		2
Sijbrands et al (2000)[26]																		2
Morcschladtet al (2004)[27]																		3
High bias assessment count× bias type	9	13	11	2	0	0	6	1	1	3	1	1	0	3	3	1	5	

White = low risk of bias; light grey = unclear risk of bias; dark grey = high risk of bias.

a concern in most studies, with 82% (23 of 28) of the attrition bias criteria and 93% (13 of 14) of the confounding bias identified as low risk.

Examining bias risk across study types also revealed trends. The registry-based studies were found to have the highest bias risk with ~30% (41 of 136) of the bias assessment criteria identified as high risk, and another 30% (41 of 136) identified as unclear risk. The hospital- and family-based studies were also found to have considerable bias risk, with 22% (19 of 85) of the bias assessment criteria identified as high risk and 29% (25/85) identified as unclear risk. Although there was only 1 population survey-based study, it performed well, with 13 of 14 bias assessment criteria reported as low risk.

Population Survey-based Studies

Benn et al[14] examined the prevalence of FH and the risk of CVD for patients with FH in a population of 69,016 individuals from the Danish general population in the Copenhagen General Population Study. This study was the only article in our review to use a general population survey approach, and it was the only study to have no areas of high-risk bias. Using a general population survey of Denmark, Benn et al applied techniques developed in the Netherlands and widely referred to as the Dutch Lipid Clinic Network Criteria. The criteria consider family and clinical CVD history, physical examination findings, and biochemical results (LDL-C) for specifying FH diagnosis.[7] They applied probabilistic diagnostic

Table II. Overview of population and registry-based studies identified in the literature review.

Study	Country/ Ethnicity	Study Sample	CVD Risk Measure	FH Risk Estimate	Exposure Group	Comparison Group
Population survey-based studies						
Benn et al (2012)[14,*]	Denmark	Population survey of 69,016 patients in Denmark	OR for CAD (fatal or nonfatal)	10.3 (7.8–13.8) 13.2 (10.0–17.4)	LMT-treated No LMT	Random sample of Danish population
Registry-based studies						
Mabuchi et al (1989)[15]	Japan	Cohort (Konazawa Hospital) of 527 vs Japanese population	PMR for CHD (fatal)	10.9 (7.95–15.03)	No LMT	Japanese population
Simon Broome Registry (1991)[16]	British	526 registry patients vs England and Wales population	SMR for CHD (fatal)[†]	3.74 (1.8–6.89) 4.13 (1.34–9.64) 3.86 (2.1–6.39)	Males (age 0–79 y) LMT-treated Females (age 0–79 y) LMT-treated All 0–79 LMT-treated	Population of England and Wales
Simon Broome Registry (1999)[17]	British	1185 registry patients (1980–1995) vs England and Wales population	SMR for CHD (fatal)[†]	2.6 (1.7–3.8)	Males (age 0–79 y) LMT-treated	Population of England and Wales
Alonso et al (2008)[18]	Spanish	811 registry patients vs Spanish population	% premature CVD (nonfatal)	8.4 (21.9%/2.6%)	80% of patients on LMT	Spanish population
Neil et al (2008)[19]	British	Simon Broome Registry, 3413 patients vs England and Wales population; 1980–1991 patients	SMR for CHD (fatal)	1.98 (1.02–3.46) 5.15 (3.35–7.64)	Primary prevention (age 20–79 y) LMT-treated Secondary prevention (age 20–79 y) LMT-treated	Population of England and Wales
		Simon Broome Registry, 3413 patients vs England and Wales population; 1992–2006 patients	SMR for CHD (fatal)	1.03 (0.75–1.38) 3.88 (3.18–4.68)	Primary prevention (age 20–79 y) LMT-treated Secondary prevention (age 20–79 y) LMT-treated	

(continued)

Table II. (continued).

Study	Country/ Ethnicity	Study Sample	CVD Risk Measure	FH Risk Estimate	Exposure Group	Comparison Group
Versmissen et al (2008)[20]	Dutch	Dutch lipid clinic patients age >55 y; N = 1950	HR for MI (nonfatal)	8.7 (4.77–15.82)	No LMT Not taking statin for >1 mo before their MI	Rotterdam study in the elderly, age/sex-matched subgroup to FH patients
				1.44 (0.80–2.60)	Primary prevention LMT-treated	
Besseling et al (2014)[21]	Dutch	High-severity FH vs low-severity FH (defining high severity in a novel way, using data from 1 subgroup and applying those data to the whole cohort). Does not provide a risk estimate vs non-FH	HR for CVD (nonfatal)	1.25 (1.05–1.51)	High severity group LMT-treated	Low severity FH group
Mundal et al (2014)[22]	Norway	Norway Registry 4688 patients (1992–2010) vs Norwegian population	SMR for CVD (fatal)	2.29 (1.65–3.19)	89.1% of patients on LMT	Norwegian population
Hospital- and family-based studies						
Jensen et al (1967)[23]	Denmark	Family study of 11 families (1944–1964 vs Danish population)	SMR (fatal)	2.88 (1.73–4.46)	LMT-treated	Danish population
Slack (1969)[24]	British	104 patients with clinical FH vs 41 patients with type III, IV, or V hyperlipoproteinemia	First MI (fatal and nonfatal)	60% increased risk	LMT-treated	Type III, IV, or V hyperlipoproteinemia
Sijbrands et al (2000)[25]	Dutch	Family study of 855 first-degree relatives vs Dutch population	SMR (fatal)	1.34 (1.16–1.55)	LMT-treated	Dutch population
Sijbrands et al (2001)[26]	Dutch	Pedigree analysis to a single pair of ancestors; 250	SMR (fatal)	1.32 (1.03–1.67)	LMT-treated	Dutch population

(continued)

Table II. (continued).

Study	Country/ Ethnicity	Study Sample	CVD Risk Measure	FH Risk Estimate	Exposure Group	Comparison Group
		descendants vs Dutch population				
Mohrschladt et al (2004)[27]	Dutch	Leiden lipid clinic patients, N = 400; all patients treated with statins	RR IHD (fatal)	2.6 (0.6–3.3)	No history of CHD LMT-treated	Dutch population

CAD = coronary artery disease; CHD = coronary heart disease; CVD = cardiovascular disease; FH = familial hypercholesterolemia; HR = hazard ratio; IHD = ischemic heart disease; LMT = lipid-modifying therapy; MI = myocardial infarction; OR = odds ratio; PMR = proportional mortality ratio; RR = relative risk. The ranges in parentheses are 95% confidence intervals.

*Only population-based estimate.

†Simon Broome standardized mortality ratio (SMR) results have been expressed as absolute risk increases (SMR/100).

criteria for the determination of FH with a modification of the Dutch Lipid Clinic Criteria, and removed factors that were not collected. The modified criteria could potentially underestimate the number of definite patients with FH and have an uncertain effect on the cardiovascular risk profile of the group as a whole. Providing a comparison group internal to the survey rather than using an external comparison group such as general population improved the validity of the comparison.

The determination of outcomes is from national patient and death registries that claim no patients are lost to follow-up.[14] The same outcome criteria are applied to both FH and non-FH, removing the likelihood of differential bias in outcomes determination. There is an unclear risk of bias in relation to whether concurrent medications or intended exposures could have modified risk. Although lipid-modifying therapies (LMTs) were considered within the study, these data were only collected at the time the survey was completed, with no information provided regarding LMT use at other times or the continuity of treatment. Use of other interventions such as diet, weight loss, and smoking cessation could not be determined. Because these are relatively minor influences on cardiovascular risk and apply to both FH and non-FH groups, however, the risk of bias is judged to be unclear. The study scored low risk on detection bias because the outcomes were a combination of fatal and nonfatal CVD. This approach is preferred to measuring only fatal events, as nonfatal events are more common and fatality from an event can be influenced by the proximity to, and quality of, care.

Registry-based Studies

Registries are a convenient and easily available data source for studying the risk of FH. The methods of recruiting patients and the comparisons made versus the general population expose these studies to important patient selection and ascertainment bias, concurrent interventions bias resulting from LMT, and challenges in controlling for confounders. Eight registry-based studies were identified in this review.

Mabuchi et al[15] examined risk of coronary heart disease in 10 homozygous and 692 heterozygous patients from 372 families in Japan. The investigators provided no description of how patients were ascertained, providing a threat to

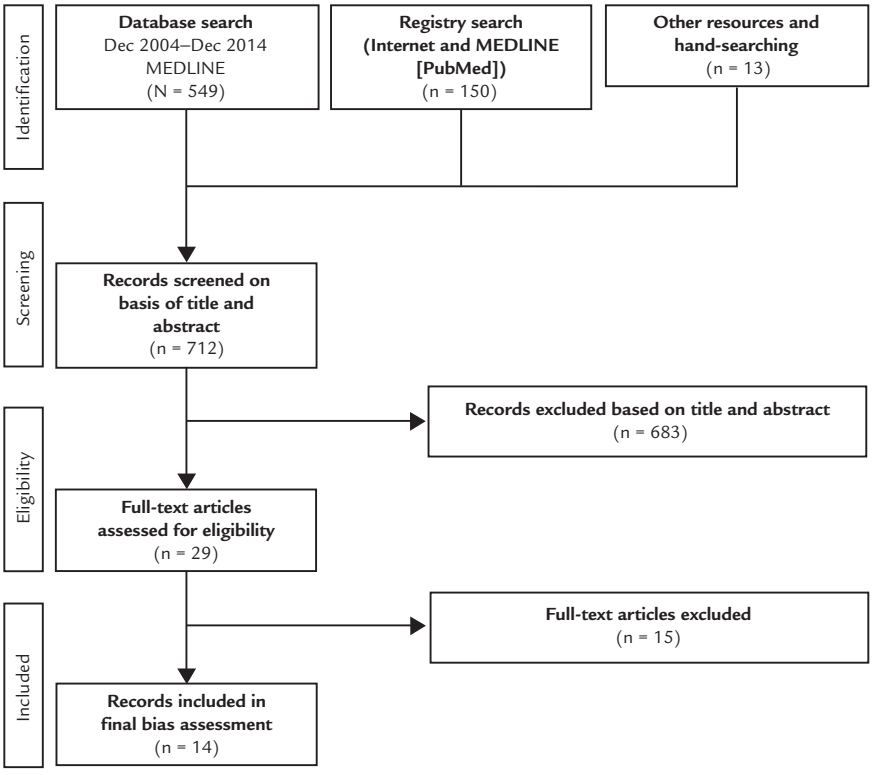

Figure 1. Preferred Reporting Items for Systematic Reviews and Meta-Analyses flow diagram for the literature review.

generalizability. This yields a high risk of bias for eligibility criteria, selection of population, and comparability of groups. Detailed clinical data were obtained from clinic records and included validated data on nonfatal cardiovascular events only, scoring a high risk of detection bias. The outcome was the proportional mortality ratio for coronary heart disease of these patients compared with that of the Japanese population. However, the investigators provided no details as to the source of the Japanese population data. It is implied that all data were collected before the availability of LMT, which is a potential strength of the study.

Three articles in this study were based on the Simon Broome Registry (1991,[16] 1999,[17] and Neil et al [2008][19]). The Simon Broome Registry itself is briefly described in the 1991 article as "beginning in 1980 with patients registered by participating lipid clinics across the UK, to which they had been referred by either general practitioners or hospital specialists." Patients are defined as having definite FH if they have a total cholesterol level >7.5 mmol/L and have tendon xanthomas themselves or in first-degree relatives. There is no other description of patient ascertainment methods in the publication, and this description is referenced by all subsequent articles. This limited methodologic description presents a serious risk of ascertainment bias given the low diagnosis rate in the United Kingdom, and the bias assessment reflects the high risk of bias in all patient recruitment-related criteria. Patients in the Simon Broome Register are treated at specialized lipid clinics but, because registry rather than clinic data are used for the publications, there is no description of specific LMT usage. Our expectation is that patients in the Simon Broome Registry are managed with the best available therapy of associated risk factors at the time of diagnosis and that this would have the effect of substantially reducing the risk of CVD and introducing high risk of performance bias. This effect is

expected to be more pronounced with longer duration of therapy, which seems to be the case as risk estimates in each of the successive Simon Broome publication exhibited lower standardized mortality ratios (SMRs) in the same patients, as well as in new patients, over time. Neil et al[19] conducted a time-based analysis of Simon Broome Registry data before December 1991 and after January 1992 to examine the effect of statin availability, recording lower SMRs in the latter group. However, the data were based on a secular trend rather than using concurrent control subjects, and there were certainly lipid- and risk-mitigating strategies available before December 1991, which affects all risk estimates from this study.

Outcome data from the Simon Broome publications[16,17,19] are determined from *International Classification of Disease, Ninth Revision*, codes from death registries, although the accuracy of these codes is potentially problematic. This scenario is particularly true for the outcome of interest (death due to CVD), in which causes of sudden death without postmortem findings are subject to uncertainty. General population registries will include patients with FH who are undiagnosed and, because the undiagnosed population in the United Kingdom is larger than the diagnosed, this method provides a source of unknown bias using this comparison group and would lower the SMR. Finally, the Simon Broome Registry data SMR estimates are highly variable within subgroups, largely because of very small sample sizes in many subgroups. In the article by Neil et al,[19] for example, observed event rates are as low as 1 to 3. Thus, the random occurrence of a single event could double or halve the calculated SMR.

Alonso et al[18] conducted a cross-sectional study on 811 patients with FH from the Spanish National FH Register to estimate the risk factors associated with the development of premature CVD. The investigators compared the results from this registry with the overall Spanish population. This article suffers from selection and detection biases, as it does not include patients who are not receiving LMT and has a small sample size. Their data yield a calculated 8.4-fold increased risk of cardiovascular risk. Some of the limitations and bias risks relating to selection bias described for the Simon Broome Registry studies[16,17] also apply here.

Versmissen et al[20] examined the efficacy of statin treatment on the risk of coronary heart disease in 2146 patients with FH recruited from 27 lipid clinics in the Netherlands by using Dutch Lipid Network criteria. The bias assessment shows a high degree of selection bias in ascertaining patients by this method, as it is possible that patients with higher severity disease are diagnosed within specialist systems. Mitigating this concern is the high degree of registration of patients in the Netherlands, with its sophisticated cascade screening programs aimed at diagnosing all patients with FH; this program results in the Netherlands having the highest FH diagnosis rates. This approach is reflected in the unclear risk score in the eligibility criteria category.

This study used detailed clinic data to determine outcomes and LMT, as opposed to "registration data" used by other studies from the Netherlands. The data on LMT are an important strength of this study, allowing the investigators to account for the effect of LMT, as well as report nonfatal events as the outcome. Risk comparison was made to patients from the Rotterdam survey, a separate data source from the lipid clinics and a potential source of bias. Although the investigators undertook an age/sex case-matched analysis, the Rotterdam study collected only MI as an outcome, with no data on angina outcomes, and also restricted their analysis to older patients (age >55 years), thus limiting comparisons versus the patients with FH. These selection and detection biases are both study weaknesses because they reduce CVD event risk in patients with FH. Indeed, a feature of the CVD risk in FH is that CVD manifests at younger ages.

Besseling et al[21] analyzed a cohort of 14,283 patients to define severe heterozygous FH and to study the cardiovascular risk factors in these patients. All data were collected at a single time point (cross-sectional analysis) for the FH-screening program in the Netherlands. The investigators used Dutch Lipid clinic data for their analysis, which has the most comprehensive cascade screening program and identified the largest number of patients with FH. These authors redefined FH severity in a way that is likely to have created a group with unknown or lower risk by applying the percentage of patients at high risk in one age group versus all other age groups. The authors then compared risk between the "newly defined" high-risk group versus the remaining "low-risk group." The effect of both methodologic decisions is likely to produce a low risk estimate. This risk of

bias is reflected in the "other biases" category of the bias assessment and is judged as a high risk of bias, in addition to high risks of bias in the familiar areas of patient selection and comparability of groups that affect other studies.

Mundal et al[22] used data obtained from the Norwegian FH registry of 4688 patients to examine if patients with FH in the statin era still have increased risk of premature cardiovascular mortality. Data were recorded at the time of registration, outcomes were determined from mortality registries, and additional data were obtained from hospital records for the 113 patients who died; the additional data included the use of LMT at time of death. Limitations of registry data as previously noted also apply to this study, including ascertainment bias and concurrent interventions bias. The limited data on LMT from hospital records of patients who died limit the analysis of treatment data. It is likely that most patients were treated with statins given the availability of these drugs during the time period of the study (1992–2010). We expect rates from this study to underestimate the true risk of CVD in FH and to better reflect the rate among patients treated for an extended time.

Hospital- and Family-based Studies

In this systematic review, 2 studies were identified on the basis of hospital data and another 3 studies on the basis of families. These methodologies are popular for studying patients with FH because of the relative ease of patient recruitment. However, compared with the population survey or registry studies, these studies have a higher degree of selection bias because patients are identified from a select and limited population. The studies suffer from selection bias with comparison groups in which the comparison groups are from a different population source.

Jensen et al[23] published one of the earlier studies that followed up 11 Danish families over time. They reported on SMR for all-cause mortality standardized according to age and sex. This study suffers from a small sample size and low numbers of events within the small sample. Also, limited information is provided on these patients and the comparison group. It can be better viewed as a description of a case series and experience over time within these patients.

The study by Slack[24] is an early trial that describes the investigator's observations of a small number of patients with type II hyperlipidemia (n = 104) and compares their event rate with similarly selected patients with types III, IV, and V hyperlipidemia (n = 41) recruited from several London hospitals. The investigator provided no formal description of the selection process for either the patients or the control subjects, which prevents generalization of the results. Formal bias assessment of this article is not favorable in a number of categories, mostly driven by the case-report nature of the publication.

Two articles by Sijbrands et al[25,26] (from 2000 and 2001, respectively) are included in this review. Both of these articles are descriptive studies of a single large family over time and compare all-cause mortality in patients with FH versus the Dutch population. These articles are limited by ascertainment bias and a lack of generalizability. In the first study,[25] the investigators evaluated 855 first-degree relatives of 113 patients who have a 50% probability of being affected, and they found that these patients are at increased risk of premature CVD. In the second study, Sijbrands et al examined the genealogy of 3 probands to a single pair of ancestors in the 19th century, then all first-degree relatives on the transmission line, finding 412 descendants, with 250 surviving $\geq$20 years. Due to inclusion criteria in these studies, ascertainment bias is a concern, as are the lack of control for confounders.

Mohrschladt et al[27] recruited 345 patients from a single clinic at the Leiden University Medical Center in the Netherlands and observed them under treatment for 8 years to determine CVD and event and mortality risk in statin-treated patients with FH. The investigators compared the mortality rate from CVD in these patients versus the general population. This study has the advantage of prospective observation with detailed data on the patients observed. However, ascertainment bias remains a concern as the patients are within a single clinic and thus reflect the practice of that specific clinic. The study is also limited by a small patient count. The estimates in this study are based on 24 patients who died of CVD. Finally, limited information is provided on the general population, such as LMT use, which is likely lower compared with these patients recruited from a clinic.

DISCUSSION

We used formal assessment of study bias to determine the least biased literature-based estimate for the elevated risk of CVD among patients with FH. This

approach has resulted in the identification of the study by Benn et al,[14] a population-level survey undertaken in Denmark. The study reported an odds ratio of 13.2 (95% CI, 10.0–17.4) for patients with FH not receiving LMTs and 10.3 (95% CI, 7.8–13.8) for patients with FH receiving LMTs, compared with patients who do not have FH and are not receiving LMT. These high odds ratios highlight the medical need in patients with FH and the need for strategies and interventions to reduce their risk of CVD.

The sources of bias identified within the reviewed studies show that bias is concentrated toward "selection bias," resulting in higher bias potential for those studies that did not reflect community or population representativeness. Obtaining a study sample that is both sufficiently sized and representative of a general population is challenging when the target disease is relatively uncommon and the event of interest within the target disease is infrequent. However, selected cohorts are more convenient and less costly to study, and they may have the advantage of higher baseline response and better follow-up, as occurs in registries.[28] Selection bias is of such importance within the formal bias assessment criteria that mitigation of this bias should occur at the study design phase of trials in which the primary objective is to find generalizable results.

Benn et al[14] undertook a population-level study in which the design included methods to appropriately sample the population to avoid ascertainment bias. The investigators used the Copenhagen General Population study, which selected individuals from the national Danish Civil Registration System to reflect the adult Danish population. Specific attention to, and acknowledgement of, the risk of ascertainment bias should be a principal study design consideration when a population risk estimate is the study objective.

The most common source of literature-based estimates of increased risk is registry-derived data. Registries in all instances were national programs designed to identify and subsequently manage patient risk. These programs are designed to identify as many patients as possible with the highest risk in the most efficient way, and then to manage their risk with the best therapies available for the remainder of the individual's life or as long as possible. Common methods were used to identify patients with early CVD, find index cases and undertake cascade family screening, and to intensify case finding within specialty settings. Although these methods are efficient and proper for registries, they result in higher bias assessments when the purpose is to understand the magnitude of increase in cardiovascular risk.

Within the studies reviewed, the duration of FH management was not directly studied. However, successive publications from the Simon Broome registries in the United Kingdom have presumably used the same initial cohort of patients augmented with additional recruitment over time. Each successive article therefore at least partly includes patients with progressively longer durations of treatment, which could have reduced the reported cardiovascular risk for FH as seen in those publications.

The odds ratio reported in the study by Benn et al[14] is within the range of ratios reported in other studies but higher than the ratios seen in estimates derived from registry studies. In particular, the risk is similar to that calculated by Versmissen et al[20] of 8.7 (4.77–15.82), which demonstrated the least amount of bias within the registry-derived studies. Versmissen et al used data from the Dutch screening program, perhaps the most successful of the global screening programs in case finding, which mitigated selection bias to some degree. They also used a close proximity comparisons group for risk calculations rather than general census data. In addition, the study by Benn et al, including the odds ratios for increased cardiovascular risk in patients with FH, is prominently featured in a European Atherosclerosis Society consensus statement (2013)[7] on guidance for clinicians to prevent coronary heart disease in patients with FH. This lends additional credibility to the study and its results as representing the best available evidence published to date, given that the only 2 studies published after the publication of this consensus statement (Mundal et al[22] and Besseling et al[21]) are shown to be limited by a high degree of selection bias as previously described.

Early articles concerning FH were well-written, descriptive observations of a new phenomenon within small groups of patients or families in which it was observed that CVD was particularly common. As occurs in much of medicine, these case descriptions are valuable in generating the hypothesis concerning the increase in risk associated with FH, and indeed the magnitude of increase in cardiovascular risk identified in these early reports left little doubt that the increase was genuine. Formal bias assessments of these studies

show that they are less useful for specific quantification of the risk.

Despite the identification of the Benn et al[14] study as having the least biased rates, there are limitations associated with the use of data from this study. The ascertainment of LMT use was through the primary survey questionnaire, which asked for LMT use at that time, but no data are provided as to the use of LMTs over time. The study by Benn et al examined the rate of a genetic disorder within Denmark. There is no evidence that FH and genetic mutations found in Denmark are different from other countries, and the advantage of the strong methods would likely overcome any bias associated with theoretical differences in genetic mutations between countries. It should be noted that Benn et al report an average CVD risk for FH versus non-FH at a population level. In clinical practice, there will be variation in severity within FH subgroups, such as those with higher or lower levels of LDL-C and other risk factors, which are important considerations for individual patient management.

All of the studies included in this review used clinical criteria, rather than genetic testing. There is therefore no distinction between homozygous and heterozygous FH and the possibility that enrolled patients might have polygenic hypercholesterolemia. Benn et al[29] have subsequently examined the mutations in 98,099 participants from their general population study and found a very high odds ratio for 4 mutations within the clinical criteria of definite and probable FH, validating the diagnostic criteria used in that study. Homozygous FH results in higher levels of LDL-C and higher cardiovascular risk, which lead to the potential of variation in results if homozygous patients are included in analyses at variable rates. Mitigating this possibility, and its effects on risk estimates, is the extreme rarity of homozygous FH, with such individuals usually coming to the attention of the health care system.

Additional limitations of this review merit consideration. We used the modified Newcastle-Ottawa criteria for bias assessment, in which there is potential low agreement between reviewers and authors.[30] Authors were not contacted for clarification of bias within this project, and assessments relied solely on the publication. Assessment of bias relied on the expertise and training of reviewers to assign levels of risk to each article after reading it. Bias assessments are therefore subject to reviewer interpretation and sometimes extrapolation from the writing within the publication. Only a single study satisfied the majority of the selection bias criteria by using a population data source. There is, therefore, lack of replication of the result in studies of the same design, and although similar risk estimates exist in studies of different design, this could occur by chance. Replication of these findings in other populations would provide greater confidence in the risk estimate. Finally, it should be noted that only publications in the English language were considered.

The effect of associated risk factors (eg, obesity, smoking, lifestyle choice) and their interaction with FH compared with their effects in the general population is not well studied within the articles reviewed. The current advice in the management of FH is to address all modifiable associated risk factors with lifestyle changes, although the benefit of this advice is likely associated with the relative magnitude of risk associated with these behaviors in patients with FH compared with those with non-FH and could be further investigated.

We have not examined the literature for the increase in risk of other cardiovascular manifestations in FH and have focused on cardiac morbidity and mortality as the most recognized source of CVD. Most of the articles in this review used "cardiovascular death" as an end point of interest, on the assumption that death was due to coronary artery disease, coronary arterial occlusion, and finally MI. The risk determined from this end point is then reported as cardiovascular risk. The effects of accelerated atherosclerosis in FH, however, are not limited to the coronary arteries. Atherosclerosis in cerebral vessels resulting in stroke tends to occur at a later age, whereas atherosclerosis in peripheral arteries leading to limb ischemia is less frequently reported overall. Both conditions are less recognized than cardiovascular disease in association with FH.

CONCLUSIONS

There are limited available data describing CVD risk in patients with FH, and many of the existing studies have biases in their study design that could affect their results. To the best of our knowledge, this review is the first to perform a bias assessment of studies reporting CVD risk in patients with FH. We found

that the only population survey-based study in our review (by Benn et al[14]) scored best for its lack of bias as a well-conducted study, providing credible estimates of the increase in CVD risk in patients with FH. The CVD risk due to FH is high and represents unmet medical need for patients with FH. Further research to assess CV risk among patients with FH using best available methods is warranted.

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AUTHOR CONTRIBUTIONS

Dr. Wong and Dr. Kruse contributed to study design, data collection, data analysis, interpretation and conclusions. Dr. Kutikova contributed to study design, interpretation and conclusions. Dr. Ray, Dr. Mata and Dr. Bruckert contributed to study interpretation and conclusions.

CONFLICTS OF INTEREST

Dr. Wong received consulting fees from Bayer, Sanofi-Aventis, Takeda, AbbVie, and Amgen; this includes consulting fees from Amgen (Europe) GmbH for the present paper. Dr. Kutikova is an employee of Amgen (Europe) GmbH and owns stock options. Dr. Ray received honoraria from Amgen, Sanofi, Regeneron, Pfizer, Aegerion, Kowa, ISIS, MSD, Lilly, and AstraZeneca as well as research grants from Pfizer, Amgen, Sanofi, and MSD. Dr. Bruckert received honoraria from Amgen, MSD, Lilly, Sanofi-Aventis, Regeneron, Aegerion, Chiesi, Danone, Unilever, AstraZeneca, and Rottapharm. Dr. Mata received honoraria and research grants from Amgen and Sanofi. The authors have indicated that they have no other conflicts of interest regarding the content of this article.

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